Original Article

The prognostic importance of red blood cell distribution width for gastric cancer: a systematic review and meta-analysis

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Background: For cancer patients, red blood cell distribution width (RDW) is a readily accessible and cost-effective preoperative prognostic predictor. This study aimed to determine whether RDW is a predictive factor for individuals undergoing radical surgery for gastric cancer (GC).

Methods: A literature search was performed to select relevant studies for inclusion in the subsequent meta-analysis. Relevant data were pooled to assess the association between RDW and GC results, including overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS), as well as clinicopathological features.

Results: The meta-analysis and systemic review included data from 8 studies comprising 1,587 individuals diagnosed with GC. In this context, RDW refers to the coefficient of variation of RDW (RDW-CV). A high level of RDW-CV was significantly associated with older age [odds ratio (OR) =2.25; 95% confidence interval (CI): 1.72–2.94; P<0.00001], larger tumor diameter (OR =1.90; 95% CI: 1.42–2.56; P<0.0001), and vascular invasion (OR =2.22; 95% CI: 1.10–4.49; P=0.03). After hazard ratios (HRs) and 95% CIs were pooled, RDW-CV was found to be an independent prognostic factor of OS (HR =1.79; 95% CI: 1.21–2.66; I^2=85%; P=0.004), DFS (HR =1.81; 95% CI: 1.37–2.39; I^2=0%; P<0.0001), and CSS (HR =2.73; 95% CI: 1.36–5.49; I^2=0%; P=0.005) in patients with GC.

Conclusions: The association between high levels of RDW-CV and poor survival in GC suggests that RDW-CV may be a viable prognostic indicator for patients with GC.

Keywords: Coefficient of variation of red blood cell distribution width (RDW-CV); gastric cancer (GC); meta-analysis; prognosis

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Introduction

Gastric cancer (GC) has become a global problem due to its hidden emergence and high mortality, with the fifth highest incidence rate and the fourth highest mortality in the world (1). Historically, surgical resection has been an effective treatment for most malignancies; however, the benefits of simple surgical resection are restricted to early GC, but the recurrence rate of advanced GC remains high (2). The survival rate of patients

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with GC may be improved with early identification and treatment; however, the application of many prognostic indicators is still controversial (3).

Red blood cell distribution width (RDW) is an indicator of blood cell count. RDW is a measurement of variation in red blood cell volume, with a higher the value indicating a greater heterogeneity of cell volume (4). RDW can be subdivided into the standard deviation of RDW (RDW-SD) and the coefficient of variation of RDW (RDW-CV), both of which are measures of red blood cell heterogeneity (5). RDW has been studied extensively in relation to various diseases, including pancreatitis (5), anemia (6), chronic obstructive pulmonary disease (7), arrhythmia, and acute myeloid leukemia (4), as well as in relation to the gastrointestinal tract.

The predictive significance of RDW in GC has been reported in a few studies (8-14), but these findings are inconsistent. In order to ascertain the predictive importance of RDW in GC, a meta-analysis was performed. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-53/rc) (15).

Methods

Systematic review registration

This meta-analysis was registered on PROSPERO (International Prospective Register of Systematic Reviews, an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome. Key features from the review protocol are recorded and maintained as a permanent record. PROSPERO aims to provide a comprehensive listing of systematic reviews registered at inception to help avoid duplication and reduce opportunity for reporting bias by enabling comparison of the completed review with what was planned in the protocol; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022378983; identifier: CRD42022378983).

Highlight box

Key findings

- The RDW-CV has important prognostic value in patients with GC.

What is known and what is new?

- There have been several studies on RDW-CV in the prognosis of GC.
- Pooling of the relevant research data indicated that RDW-CV can be used as an important prognostic factor for GC.

What is the implication, and what should change now?

- RDW-CV can have additional predictive ability for patients with GC when included in clinical decision-making.

Literature search

On November 3, 2022, S Yan and J Kong searched for relevant materials in 4 databases (Embase, Web of Science, PubMed, and Cochrane Library). The retrieval strategy for PubMed was as follows: (Stomach Neoplasms or Neoplasm, Stomach or Stomach Neoplasm or Neoplasms, Stomach or Gastric Neoplasms or Gastric Neoplasm or Neoplasm, Gastric or Neoplasms, Gastric or Cancer of Stomach or Stomach Cancers or Gastric Cancer or Cancer, Gastric or Cancers, Gastric or Gastric Cancers or Stomach Cancer or Cancer, Stomach or Cancers, Stomach or Cancer of the Stomach or Gastric Cancer, Familial Diffuser) and (red blood cell distribution width or RCDW or RDW or RDW-CV or RDW-SD or red cell distribution width). The retrieval strategy was based on medical subject heading (MeSH) terms and title/abstract terms, while the retrieval strategy of other databases was based on the retrieval features of each database (for details of the retrieval, please see Appendix 1). In addition, the reference citations of the included literature were manually retrieved to ensure a comprehensive literature retrieval. The retrieved pieces of literature were introduced into EndnNoteX9 (Clarivate, London, UK) to delete duplicates and screen eligible studies.

Inclusion and exclusion criteria

The following were the inclusion criteria for the literature: (I) GC patients received radical surgery; (II) preoperative RDW-CV examination data were available; and (III) data on overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS) were available or could be derived through other data. The exclusion criteria were as follows: (I) repeated literature, comments, conference abstracts, and case reports; and (II) incomplete relevant data, such as lack of prognostic data (OS, DFS, and CSS) or RDW-CV value.

Selection process

S Yan and J Kong independently screened the literature. First, the titles and abstracts of the retrieved materials were examined for preliminary screening. Second, to assess whether the remaining content was appropriate for inclusion or elimination, the full text was read. If there were conflicts concerning literature selection, the two authors discussed the case to arrive at a resolution.

Data extraction

S Yan and ZF Zhao separately extracted data from the included materials. Article information including first author, country of publication, publication year, and time period of research was retrieved. The retrieved data included RDW type, sample size, RDW cutoff value, and the prognostic data of patients with GC, including OS, DFS, and CSS. From the included studies, data on age, gender, tumor diameter, tumor depth, lymph node metastasis, pathological stage (pStage), and vascular invasion were collected separately by S Yan and ZF Zhao, who then double-checked each other's work and then sent it to H Yao for further inspection and verification of the data's validity.

Quality assessment

S Yan and J Kong independently assessed the quality of the included studies using the Newcastle-Ottawa Scale (NOS). Of these, works scoring 9 represented literature of the highest quality, those scoring 7–8 represented moderate quality, and those scoring 6 or less represented the lowest quality. Differences in rating between S Yan and J Kong were reconciled through discussion.

Statistical analysis

RevMan 5.4 (Cochrane, London, UK) software was employed for this meta-analysis. First, pooled hazard ratios (HRs) and 95% CIs were used to analyze the relationship between RDW-CV and prognostic markers (OS, CSS, and DFS) in GC. Following this, the pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to analyze the relationship between RDW-CV and the clinicopathological features in GC. Finally, the statistical heterogeneity was calculated using the chi-squared test and the I^2 value. According to a fixed effects model, $I^2 \leq 50\%$ indicated low heterogeneity, whereas according to a random effects model, $I^2 > 50\%$ indicated strong heterogeneity; $P \leq 0.05$ indicated statistical significance. Sensitivity analysis was used to evaluate the stability of the results by eliminating the results one by one; that is, the influence of each study on the overall results was removed so as to evaluate the robustness of the synthesized results.

Results

Study selection

From the four databases searched, 157 publications were retrieved, including 82 from Embase, 47 from Web of Science, 24 from PubMed, and 4 from Cochrane Library. After layers of screening were applied, 7 studies were finally included for meta-analysis. The screening flowchart is shown in *Figure 1*.

Study characteristics

There were 1,587 patients with GC in the 7 articles included in this meta-analysis. It is worth noting that Cheng *et al.*'s [2017] study included 2 sets of data related to RDW-CV in patients with GC (8). Therefore, a total of 8 studies were ultimately included. There were 4 studies from China, 2 from Japan, and 1 from Turkey, with the publication years ranging from 2017 to 2021 and the research years spanning from 2005 to 2016. Based on the RDW-CV cutoff value, all patients with GC were separated into two categories. *Table 1* shows the basic characteristics of the included studies and their NOS scores.

RDW-CV and clinicopathological characteristics

Additional data were gathered from patients before the pooling of the ORs and 95% CIs, and the pooling results of data related to clinicopathological features were as follows. High levels of RDW-CV were significantly associated with older age (OR =2.25; 95% CI: 1.72–2.94; P<0.00001; *Figure 2A*). The level of RDW-CV had a low association with gender (OR =1.03; 95% CI: 0.78–1.35; P=0.86; *Figure 2B*). A high level of RDW-CV was more associated with longer tumor diameter as compared to a low level of RDW-CV (OR =1.90; 95% CI: 1.42–2.56; P<0.0001; *Figure 2C*). Of the included studies, 2 involved the relationship between RDW-CV level and the depth of tumor invasion, but no link was found between the two factors (OR =0.98; 95% CI: 0.08–11.55; P=0.99; *Figure 2D*).

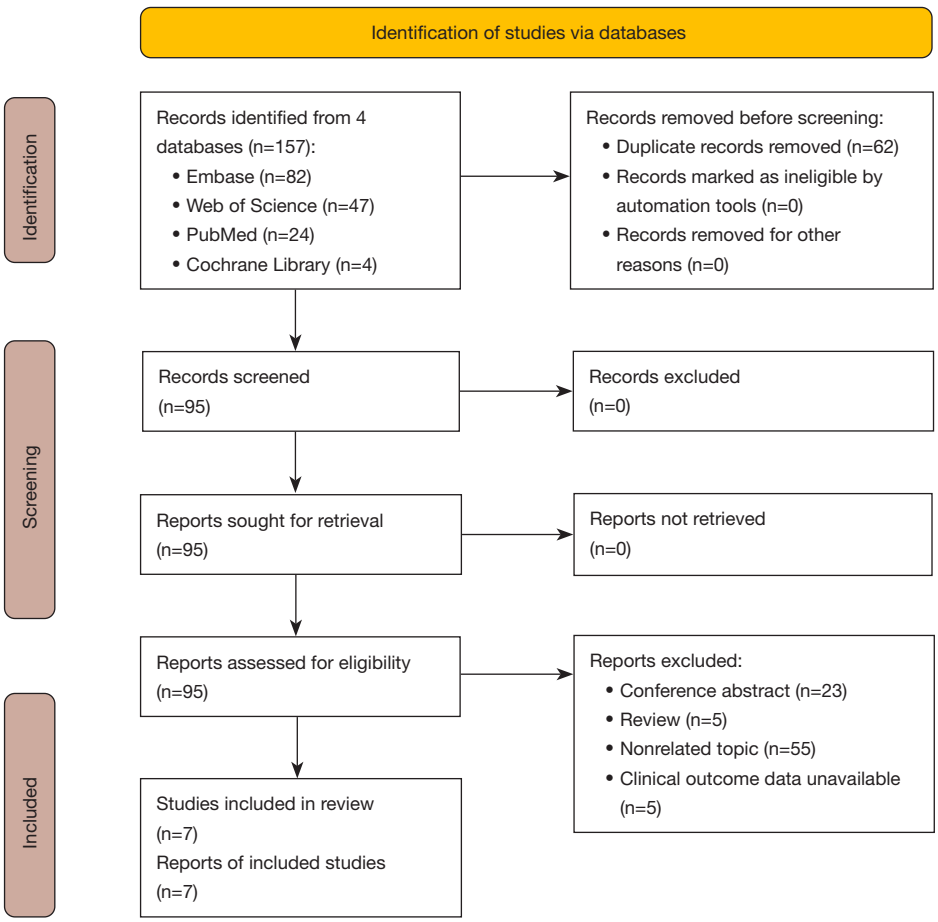

Figure 1 Flowchart of study screening.

Table 1 Baseline characteristics of included studies

First author	Country	Year	Study date	RDW type	Sample size	Cutoff volume (%)	Clinical outcome	NOS
Cheng S	China	2017	2010–2014	RDW-CV	227	13.00	OS/DFS	8
Cheng S	China	2017	2010–2014	RDW-CV	164	12.85	OS/DFS	8
Yazici P	Turkey	2017	2009–2015	RDW-CV	172	16.00	OS	8
Zhou D	China	2018	2012–2016	RDW-CV	103	13.40	OS/DFS	7
Cui MT	China	2020	2006–2016	RDW-CV	104	12.90	OS	8
Shota S	Japan	2020	2005–2013	RDW-CV	221	14.85	OS/CSS	7
Fu L	China	2021	2014–2015	RDW-CV	151	14.10	OS/DFS	7
Saito H	Japan	2021	2005–2013	RDW-CV	445	14.25	OS/CSS	8

RDW, red blood cell distribution width; NOS, Newcastle-Ottawa Scale; RDW-CV, coefficient of variation of red blood cell distribution width; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival.

Similarly, there was no relationship found between RDW-CV level and lymph node metastasis in GC in the three applicable studies (OR =0.98; 95% CI: 0.45–2.15; P=0.96; *Figure 2E*), and this was also the case for the postoperative pStage of patients with GC (OR =1.22; 95% CI: 0.55–2.70; P=0.63; *Figure 2F*). However, in 2 studies, the pooled results showed that patients with GC and low levels of RDW-CV had a shallower or lower likelihood of vascular invasion (OR =2.22; 95% CI: 1.10–4.49; P=0.03; *Figure 2G*). The heterogeneity of some clinicopathological parameters was large. When I^2>50%, a random effects model was applied, while when I^2≤50%, a fixed effects model was applied; more information can be found in *Table 2* and *Figure 2*.

RDW-CV and clinical outcome indicators

Results of the RDW-CV correlation with OS were reported in 7 of the included studies, with DFS being reported in 3 and CSS being reported in 2. Compared to patients with GC and a high level of RDV-CV, those with a low level of RDW-CV had more favorable OS, DFS, and CSS. RDW-CV was found to be an independent prognostic marker for the following outcomes: OS (HR =1.79; 95% CI: 1.21–2.66; I^2=85%; P=0.004; *Figure 3A*), DFS (HR =1.81; 95% CI: 1.37–2.39; I^2=0%; P<0.0001; *Figure 3B*), and CSS (HR =2.73; 95% CI: 1.36–5.49; I^2=0%; P=0.005; *Figure 3C*). After the effect size of RDW-CV and the OS-related studies was pooled, the results suggested high heterogeneity, so a random effects model was applied (I^2=85%; P<0.00001).

Sensitivity analysis

The meta-analysis was repeated by excluding each included study one by one and then pooling the effect size; excluding any study did not significantly change the final results. In particular, due to the small number of included studies (fewer than 10), no analysis of publication bias was conducted.

Discussion

This meta-analysis gathered all available research on the predictive value of RDW for patients with GC by searching 4 databases (Embase, Web of Science, PubMed, Cochrane Library). Following the first screening, 7 articles and 8 studies were included, resulting in data from 1,587 patients with GC. For this meta-analysis, the total sample size was relatively small. Based on the analysis of the included studies, it is clear that all of the original studies were conducted at local medical institutions, which are small clinical medical centers, where the number of patients and the staff dedicated to working in clinical studies may be small, resulting in a small sample size for each original study itself. When the HRs and 95% CIs from the included studies were combined, it was discovered that RDW-CV was substantially associated with the prognosis of patients with GC; specifically, a high level of RDW-CV was linked with poor OS, DFS, and CSS. A strong association was also found between RDW-CV and other clinicopathological features of patients with GC, including age, tumor diameter, and tumor vascular invasion.

Previous research on RDW as a prognosis factor for GC is conflicting. Some studies reported that RDW-CV is a predictive predictor for the OS of patients with GC (10,12-14), while others did not find this to be the case (8,9,11). Similarly, in 1 study, RDW-CV was found to not be a reliable predictor for the DFS patients with GC (10), although 2 other studies reported the opposite (8,13). This meta-analysis was conducted to determine if RDW-CV impacts the prognosis of patients with GC.

Compared to other GC prognostic indicators, such as long noncoding RNA (lncRNA), microRNA, and protein markers (16-18), RDW is a simple and inexpensive metric that indicates the degree of red blood cell volume heterogeneity (19). RDW was commonly employed in diagnosing anemia (6), but as research has progressed, RDW has become more prevalent in diagnosing human disorders. Patients with colorectal cancer with high RDW levels have been observed to have a poor prognosis (20,21). Patients with breast and lung cancer have a higher risk of death and postoperative recurrence when their RDW is high (22,23). Similarly, a higher level of RDW has impacted the survival of those with multiple myeloma (24). A substantial, favorable, and independent correlation between RDW and traditional inflammatory biomarkers has been demonstrated (25). Additionally, various proinflammatory cytokines limit erythropoietin production or function, and an increase in RDW results from inflammation (26). Moreover, inflammation is present in almost every human malignancy, which helps to explain why RDW values rise in cancer patients on average and provides support for RDW's use as a biomarker of the prognosis of those with cancer (27). Notably, this meta-analysis's findings corroborate those of several other studies reporting that RDW increases with age (28). In addition, medium- and long-distance runners, as well as pregnant women in their latter trimesters, have

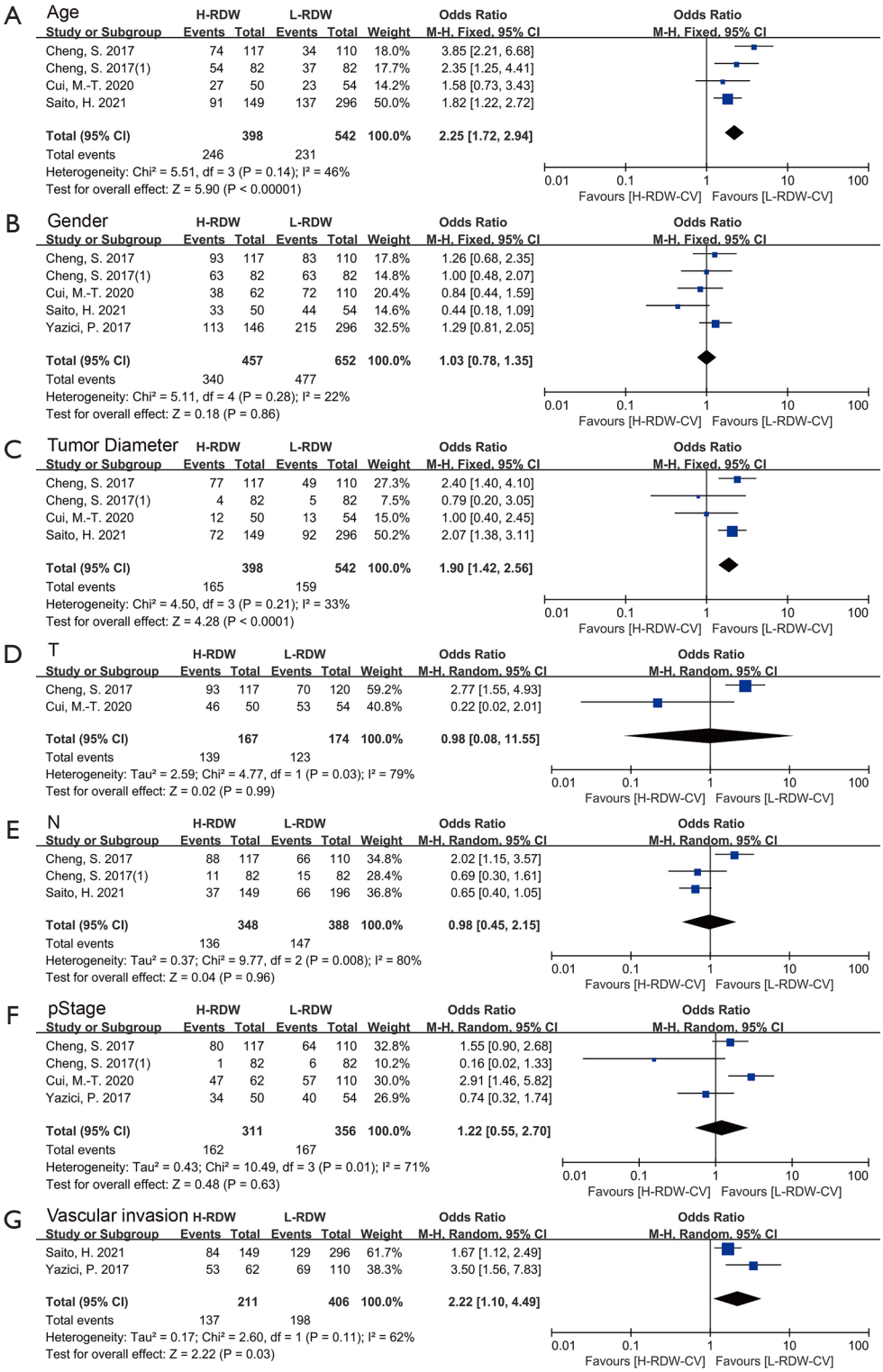

Figure 2 Forest plot illustrating the relationship between RDW-CV and clinicopathological traits. (A) Age. (B) Gender. (C) Tumor diameter. (D) Tumor depth. (E) Metastasis to lymph nodes. (F) pStage. (G) Vascular invasion. H-RDW, high level of red blood cell distribution width; L-RDW, low level of red blood cell distribution width; M-H, Mantel-Haenszel; CI, confidence interval; RDW-CV, coefficient of variation of red blood cell distribution width; pStage, pathological stage.

Table 2 The correlation between RDW-CV and clinicopathological characteristics in patients with GC

Characteristics	Number of studies	Number of patients	Pooled OR (95% CI)	P value	Heterogeneity		
					I^2 (%)	P value	Model
Age (years) (old *vs.* young)	3	940	2.25 (1.72–2.94)	<0.001	46	0.14	Fixed
Gender (male *vs.* female)	4	1,109	1.03 (0.78–1.35)	0.86	22	0.28	Fixed
Tumor diameter (cm) (large *vs.* small)	3	940	1.90 (1.42–2.56)	<0.001	33	0.21	Fixed
Depth of tumor (T3 + T4 *vs.* T1 + T2)	2	331	0.98 (0.08–11.55)	0.99	79	0.03	Random
Lymph node metastasis (N1 + N2 + N3 *vs.* N0)	2	736	0.98 (0.45–2.15)	0.96	80	0.008	Random
pStage (III + IV *vs.* I + II)	3	667	1.22 (0.55–2.70)	0.63	71	0.01	Random
Vascular invasion (present *vs.* absent)	2	617	2.22 (1.10–4.49)	0.03	62	0.11	Random

RDW-CV, coefficient of variation of red blood cell distribution width; GC, gastric cancer; OR, odds ratio; CI, confidence interval; pStage, pathological stage.

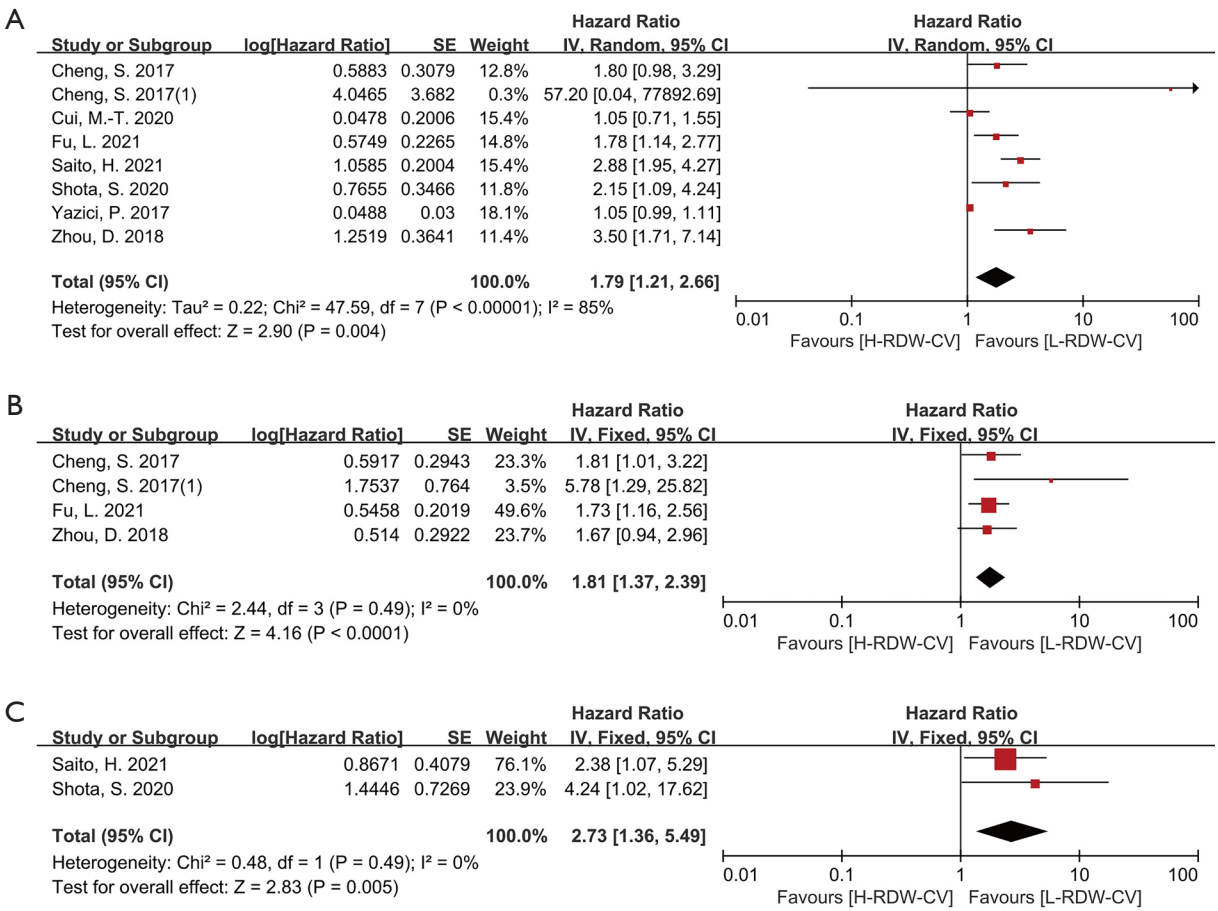

Figure 3 Forest plot of the relationship between RDW-CV and clinical prognostic indicators. (A) RDW-CV and OS. (B) RDW-CV and DFS. (C) RDW-CV and CSS. SE, standard error; CI, confidence interval; H-RDW, high level of red blood cell distribution width; L-RDW, low level of red blood cell distribution width; RDW-CV, coefficient of variation of red blood cell distribution width; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival.

shown to have elevated RDW (29-31); therefore, this observation should be considered during clinical evaluation.

Some limitations to this meta-analysis should be addressed (I) the number of included studies was relatively low, with a total of fewer than 10, and the sample size of each study was also small, as was the overall sample size after aggregation. (II) Due to the fact methods, instruments, experimenters, laboratory standards, and statistical methods for measuring the red blood cell size varying across different laboratories, no universal reference range exists (32,33). Inconsistent cutoff values of classified for data related to RDW-CV, age, or tumor diameter, may lead to inaccurate results after analysis. (III) Not all the included studies reported clinical outcome indicators, further reducing the amount of data used for statistical analysis.

Nonetheless, we concluded that RDW-CV could be an independent prognostic marker for OS, DFS, and CSS in patients with GC.

Conclusions

In this study, after a database search for relevant literature, 7 articles (8 studies) were included in the meta-analysis. The results showed that RDW-CV was closely related to the prognosis of patients with GC, and those with a low level of RDW-CV had more favorable OS, DFS, and CSS. In addition, RDW-CV was also related to the age, tumor diameter and tumor vascular invasion in GC patients. RDW-CV can be used as an independent prognostic factor and can have additional predictive ability in clinical decision-making for patients with GC.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-53/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-53/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-53/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1

Search strategy

Databases—PubMed, Embase, Web of Science Strategy, and Cochrane Library Limits: publications until November 3, 2022.
(I) PubMed
((((((((((((((((((((Stomach Neoplasms[MeSH Terms])) OR (Neoplasm, Stomach[Title/Abstract])) OR (Stomach Neoplasm[Title/Abstract])) OR (Neoplasms, Stomach[Title/Abstract])) OR (Gastric Neoplasms[Title/Abstract])) OR (Gastric Neoplasm[Title/Abstract])) OR (Neoplasm, Gastric[Title/Abstract])) OR (Neoplasms, Gastric[Title/Abstract])) OR (Cancer of Stomach[Title/Abstract])) OR (Stomach Cancers[Title/Abstract])) OR (Gastric Cancer[Title/Abstract])) OR (Cancer, Gastric[Title/Abstract])) OR (Cancers, Gastric[Title/Abstract])) OR (Gastric Cancers[Title/Abstract])) OR (Stomach Cancer[Title/Abstract])) OR (Cancer, Stomach[Title/Abstract])) OR (Cancers, Stomach[Title/Abstract])) OR (Cancer of the Stomach[Title/Abstract])) OR (Gastric Cancer, Familial Diffuse[Title/Abstract])) AND ((((((red blood cell distribution width[Title/Abstract]) OR (RCDW[Title/Abstract])) OR (RDW[Title/Abstract])) OR (RDW-CV[Title/Abstract])) OR (RDW-SD[Title/Abstract])) OR (red cell distribution width[Title/Abstract]))

(II) Embase
#1: 'stomach cancer'/exp OR (cancer AND of AND the AND cardia) OR (cancer AND of AND the AND gastric AND antrum) OR (cancer AND of AND the AND gastric AND body) OR (cancer AND of AND the AND gastric AND cardia) OR (cancer AND of AND the AND gastric AND fundus) OR (cancer, AND stomach) OR (cardia AND cancer) OR (gastric AND antral AND cancer) OR (gastric AND antrum AND cancer) OR (gastric AND body AND cancer) OR (gastric AND cancer) OR (gastric AND cardia AND cancer) OR (gastric AND cardiac AND cancer) OR (gastric AND malignancies) OR (gastric AND malignancy) OR (malignancies AND of AND the AND stomach) OR (malignancy AND of AND the AND stomach) OR (malignant AND gastric AND neoplasm) OR (malignant AND gastric AND tumor) OR (malignant AND neoplasm AND of AND the AND stomach) OR (malignant AND neoplasms AND of AND the AND stomach) OR (malignant AND tumor AND of AND the AND stomach) OR (malignant AND tumors AND of AND the AND stomach) OR (malignant AND tumour AND of AND the AND stomach) OR (malignant AND tumours AND of AND the AND stomach) OR (pyloric AND cancer) OR (stomach AND malignancies) OR (stomach AND malignancy)
#2: red AND blood AND cell AND distribution AND width OR (red AND cell AND distribution AND width) OR rcdw OR rdw OR 'rdw cv' OR 'rdw sd'
#3: #1 AND #2

(III) Web of Science
TS = (Stomach Neoplasms OR Neoplasm, Stomach OR Stomach Neoplasm OR Neoplasms, Stomach OR Gastric Neoplasms OR Gastric Neoplasm OR Neoplasm, Gastric OR Neoplasms, Gastric OR Cancer of Stomach OR Stomach Cancers OR Gastric Cancer OR Cancer, Gastric OR Cancers, Gastric OR Gastric Cancers OR Stomach Cancer OR Cancer, Stomach OR Cancers, Stomach OR Cancer of the Stomach OR Gastric Cancer, Familial Diffuse) and TS = (red blood cell distribution width OR RCDW OR RDW OR RDW-CV OR RDW-SD OR red cell distribution width)

(IV) Cochrane Library
((Cancer, Gastric) OR (Cancers, Stomach) OR (Gastric Cancers) OR (Cancers, Gastric) OR (Stomach Cancer) OR (Cancer of the Stomach) OR (Gastric Cancer) OR (Neoplasm, Gastric) OR (Stomach Neoplasm) OR (Neoplasms, Stomach) OR (Gastric Neoplasms) OR (Neoplasm, Stomach) OR (Neoplasms, Gastric) OR (Gastric Neoplasm) OR (Stomach Neoplasms) OR (Gastric Cancer, Familial Diffuse) OR (Stomach Cancers) OR (Cancer of Stomach) OR (Cancer, Stomach)) AND ((red blood cell distribution width) OR (red cell distribution width) OR (RCDW) OR (RDW) OR (RDW-CV) OR (RDW-SD))

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